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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,466	03/31/2000	UGO RIPAMONTI	STK-6	2489

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/540,466	RIPAMONTI ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-29* is/are pending in the application.

4a) Of the above claim(s) *22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Election filed May 28, 2003 (Paper No. 20) in response to the Office Action of April 2, 2003 is acknowledged and has been entered.

Claims 21-29 are pending in the application.

Claims 22-25 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 21, and 26-29 are currently under prosecution

Applicants have elected with traverse a method of inducing angiogenesis using a dimeric OP-1 as a morphogenic protein. This election will now be considered as Group 18 since OP-1 is the first dimeric protein listed in Claim 27 of the linking claims. The traversal is on the ground(s) that Claim 21, which is a linking claim for each of Groups 1-17 and 18-23, is also a linking claim for the monomeric and dimeric morphogenic proteins. Applicants argue that administration of the morphogenic protein links monomeric and dimeric forms of the morphogenic proteins. This argument has been considered but is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 18. Furthermore, the administration of monomeric and or dimeric proteins constitutes materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. Also, the literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search.

Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

Claim 27 is objected to for reciting "BMP-5, BMP-6, BMP-8, GDF-6, and GDF-7" as being drawn to non-elected groups.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a dimeric species comprising a polypeptide selected from the group consisting of OP-1, and therefore the written description is not commensurate in scope with the claims drawn to amino acid sequence variants of OP-1, which read on naturally occurring allelic variants.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Alleles are known in the art as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome and differing from other alleles of that locus at one or more mutational sites which encode allelic variant proteins. Thus, in this case, the structure of naturally occurring allelic sequences are not defined, nor is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of OP-1, the skilled artisan cannot envision the detailed structure of the encompassed variant polypeptides (including those with the same functional activity) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a

genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore, only the dimeric species consisting of OP-1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 26, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Eriksson *et al.* (US Patent No. 5,840,693, November 1998).

The claims are drawn to a method for inducing angiogenesis in a mammal by administering an effective amount of a morphogenic protein; with the proviso that said morphogenic protein is not BMP-2 or GDF-5 (Claim 21); wherein the morphogenic protein comprises a disulfide bonded dimeric species (Claim 26); wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell (Claim 29).

It is noted that the specification does not limit the term of what is included or excluded as a morphogenic protein only that said protein has morphogenic activity (page 13, line 24) wherein

said activity can refer to ability of an agent to stimulate a target cell to proliferate that may optionally lead to cell differentiation (page 14, line 25). **Hence, the claims are broadly interpreted to include any protein that induces endothelial cell proliferation and or angiogenesis wherein said protein comprises a disulfide bonded dimeric species.**

Eriksson *et al.* teach a novel growth factor (i.e. a morphogenic protein) referred to as vascular endothelial growth factor B or VEGF-B (column 4, line 3). Eriksson *et al.* further teach that VEGF-B proteins can be used in clinical methods to accelerate angiogenesis in wound healing (column 4, line 15), or to promote angiogenesis during development of the corpus luteum and endometrium as an aid to initiating and or maintaining pregnancy (column 29, lines 12+). Further, VEGF-B may be produced by the expression of a recombinant DNA molecule in a host cell to provoke an angiogenic response in order to treat tissue ischemia (column 30, line 5). The authors further teach that VEGF-B includes a protein dimer comprising VEGF-B protein, particularly a disulfide-linked dimer (column 4, line 58; column 66, line 10).

Claims 21, 26 and 29 are further rejected under 35 U.S.C. 102(b) as being anticipated by Connolly *et al.* (US Patent No. 5,008,196, April 1991).

Connolly *et al.* teach a morphogenic protein wherein said protein comprises a disulfide bonded dimeric species (abstract; column 2, line 12). Connolly *et al.* further teach that said morphogenic protein can be used to stimulate endothelial cell growth (i.e. angiogenesis) by administration to a patient in need of such treatment such as, for example, as may be need for mitogenic activity in would healing (column 10, lines 58+). Connolly *et al.* further teach that

said morphogenic protein is produced by the expression of recombinant DNA in a host cell (column 3, lines 1-33).

Claims 21, and 26-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Israel *et al.* (WO 93/09229, IDS).

The claims are drawn to a method for inducing angiogenesis in a mammal by administering an effective amount of a morphogenic protein; with the proviso that said morphogenic protein is not BMP-2 or GDF-5 (Claim 21); wherein the morphogenic protein comprises a disulfide bonded dimeric species (Claim 26); wherein the dimeric species comprises a polypeptide consisting of OP-1 and or amino acid sequence variants thereof (Claim 27); the method according to Claim 21 wherein the morphogenic protein is OP-1 (Claim 28); wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell (Claim 29).

Israel *et al.* teach (page 12, lines 2 and 20) recombinant expression of morphogenic proteins in host cells, including disulfide bonded dimeric BMP-7 (OP-1 is also referred to as BMP-7; specification page 6, line 24). Israel *et al.* further teach that the heterodimeric proteins are capable of stimulating the growth of bone forming cells (page 35), inducing differentiation of progenitors of bone-forming cells, and increasing neuronal survival. Further, Israel *et al.* teach that such dimeric proteins have a variety of therapeutic and pharmaceutical uses such as administration of the proteins to patients for the purposes of wound healing and bone repair. Thus, while Israel *et al.* do not characterize BMP-7 as angiogenic, the claimed functional limitation would be an inherent property of the referenced method since the specification

discusses (page 2, line 15) that various physiological processes *require* angiogenesis, including wound healing and bone repair. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Hence, even though the claims are drawn to a mechanism by which the disulfide bonded dimeric OP-1 induces mammalian angiogenesis, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
July 31, 2003